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ALTERATIONS IN TISSUE METABOLISM (THE LUNG) WITH INJURY AND SHOCK

Annual Summary Report

Arthur E. Baue, M.D.

July 15, 1972

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Washington University School of Medicine

and

The Jewish Hospital of St. Louis
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In a short period of time ~~we have thus found~~ were found to occur a number of changes, ~~occurring~~ in cells with shock which are progressive. These are original observations which are now being confirmed by other investigators. ~~We are presently relating~~ These changes to other things which are occurring in the cell and ~~to how they~~ affect organ failure. This is now beginning to lead to study of treatment programs ~~as~~ and ~~they~~ influence depressed cell function. A more coherent story of how cells deteriorate and how function can be improved by treatment is being developed.

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During the contract year we have continued to study extensively alterations in cell function with shock and hypoxia. All the details of our previous work will not be given but only a description of the pertinent highlights during the past year in three general, related areas.

A. We have now looked into alterations in adenosine nucleotides in hemorrhagic shock. Decreased respiratory activity of mitochondria in shock previously demonstrated by us and by other investigators has suggested limitations in the capability to synthesize ATP. Whether or not this results in decreased levels of ATP with shock has not been shown conclusively. For this purpose, albino Holtzman rats, fasted for sixteen hours were bled while awake to a mean arterial pressure of 40 mm Hg which was maintained for two hours. After sacrifice, liver, kidney and soleus muscle were quickly removed and frozen. A protein free extract was made and analyzed enzymatically for the nucleotides. Six bled and six unbled animals were compared. The data clearly demonstrated a drastic reduction in ATP with shock which must be due to decreased biosynthesis. Concommittant decreases in ADP and AMP and the increase in inorganic phosphate indicate a non-specific hydrolysis of the nucleotides as well. Maintenance of normal glucose-6-phosphate levels with shock suggests that the glycolytic system was intact. Thus there is a substantial decrease in energy availability in the tissue studied with severe shock.

   An abstract of this work which has been sent for publication is enclosed.

B. We have completed an initial and fairly extensive study by Dr. Jerry Meyers, John Meyer and me in which shock was produced after heparinization by rapid bleeding into airless plastic bags or open plastic reservoirs to a mean arterial pressure of 30 or 40 mm Hg for two hours in thirty dogs without heart worms, 21 from a farm and nine from a dog pound. Blood was returned rapidly or slowly by vein or artery. In five a respirator was used; others breathed room air spontaneously; half received antibiotics; seven were studied awake; others were anesthetized. Femoral and pulmonary artery pressures, P_{O_2}, P_{CO_2} and pH were measured every fifteen minutes to three hours post-reinfusion. Blood gases were then measured daily. Animals were sacrificed after shock or

reinfusion or at intervals to five days. Descriptions of the lungs were recorded in situ and microscopy was carried out after expanding one lung with buffered formalin and fixing the other in a non-expanded state. In 25 of these dogs there was no hypoxia and the lungs were grossly and microscopically indistinguishable from unbled animals with no intra-alveolar fluid, hemorrhage, membranes, septal edema, disruption or atelectasis. Four had only small localized changes. One had severe hemorrhage in one lobe due to a pulmonary thrombus and was the only animal with hypoxia before bleeding. No animal had any evidence of generalized hemorrhage or consolidation. No impairment of respiratory function or significant or consistent morphologic changes were found in lungs of dogs subjected to hemorrhagic shock. The changes found previously by other investigators must then be due to factors other than shock itself. Definition of these factors is being carried out and may help to clarify the problem of post-traumatic pulmonary insufficiency.

This work is now being extended in the laboratory. An abstract of this work is enclosed which has been sent for publication.

C. We have studied further the failure of active transport of cation in hemorrhagic shock. These initial studies were carried out primarily in the liver. Studies of cations in the red blood cells and skeletal muscle transmembrane potentials in hemorrhagic shock suggest alteration in sodium pump activity with shock. We have measured the capability of liver slices of shocked animals to carry out active transport of sodium and potassium. Liver slices from rats in late shock bled to 40 mm Hg arterial pressure until 70% of oxygenated Krebs-Ringer's bicarbonate at 0.5°C for 90 minutes to allow passive diffusion of potassium out and sodium into cells and then at 37°C for one hour. Sodium and potassium of dry tissues of the liver slices were measured. A decrease in sodium and an increase in potassium on rewarming the tissue from 0.5 to 37°C in control liver slices indicated reactivation of the transport mechanism. In late shock sodium contents increased instead of decreasing the potassium remained unaltered. These data clearly indicate failure of the sodium pump mechanism in late shock.

This work is also now being extended to measure more exactly intra- and extracellular contents and the reasons for these changes will be further investigated. An abstract of this work is enclosed.

In a short period of time we have thus found a number of changes occurring in cells with shock which are progressive. These are original observations which are now being confirmed by other investigators. We are presently relating these changes to other things which are occurring in the cell and to how they effect organ failure. This is now beginning to lead to study of treatment programs as they influence depressed cell function. A more coherent story of how cells deteriorate and how function can be improved by treatment is being developed.

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